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(54) Use of rapamycin and derivatives and prodrugs thereof in the manufacture of a medicament for inhibiting transplant rejection in mammals

Verwendung von Rapamycin, dessen Derivaten und Prodrugs zur Herstellung eines Arzneimittels zur Hemmung der Transplantatabstossung bei Säugetieren

Utilisation de la rapamycine ou ses dérivés ou précurseurs pour l'obtention d'un médicament destiné à empêcher le rejet de greffes chez les mammifères

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- **INTERNATIONAL ORGAN TRANSPLANT FORUM, Pittsburg, Pennsylvania, 8th - 11thSeptember 1987, vol. 20, no. 1, suppl. 1, pages 209-214; T. OCHIAI et al.:"Studies on FK506 in experimental organ transplantation"**
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- **PHARMACOLOGICAL REVIEWS, vol. 41, No. 3, 1989, p. 239-242 (Borel et al.)**
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- **PHYSICIANS' DESK REFERENCE, 1988, p. 1879-1881**
- **PHYSICIANS' DESK REFERENCE, 1989, p. 1892-1894**
- **ABPI DATA SHEET COMPENDIUM 1988-1989, p.1342-1344**

Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

Description

This invention relates to the use of rapamycin for the preparation of a medicament for inhibiting organ or tissue transplant rejection in mammals.

Rejection and infective complications resulting from immunosuppressive treatment are the principal causes of failure of organ allografting in man, that is, an organ graft made between two genetically different individuals in the same Homo sapiens species. In order to minimize the individual specific side-effects of the three effective agents used in clinical practice, namely azathioprine, corticosteroids and cyclosporin, small doses of each are used in combination "triple therapy". Of the three agents currently used in such triple therapy, cyclosporin is the most powerful, but has the unsatisfactory side-effect of nephrotoxicity in man which can lead to structural renal damage. Increased corticosteroid dosage and antilymphocyte antibody preparations, poly- or monoclonal, are used for the treatment of rejection crises. A number of studies have been taken to investigate other potentially effective compounds for use as immunosuppressants and transplant rejection inhibitors, but to date, none have been found to be useful in clinical settings because of side-effects, such as toxicity, the lack of efficacy or a combination of these factors.

The fungal product FK506 was reported to have immunosuppressive activity in animals with organ grafts (Ochiai, T., et al., Transplant. Proc., Vol. XX, No. 1, pp. 209-214, 1988). Although the immunosuppressive activity of FK506 was confirmed, the toxicity in mammals, such as rats, pigs and dogs, and in primates, e.g., baboons, was too severe to proceed to clinical phase trials (Collier, D. St. J., et al., Transplant. Proc., Vol. XX, No. 1, pp. 226-228, 1988).

It would be extremely useful to discover a compound having immunosuppressive activity which could be employed to increase transplant acceptance in a recipient but without causing serious toxic side effects typically associated with conventional immunosuppressant therapy, such as those discussed above.

Rapamycin is a lipophilic macrolide with certain structural similarities to FK506 produced by Streptomyces hygroscopicus with both antifungal and antitumor properties (Sehgal, S.N. et al., J. Antibiot., Vol. 28, pp. 727-732, 1975; Eng. C.P., et al., J. Antibiot., Vol. 37, pp. 1231-1237, 1984).

It was reported that rapamycin inhibited two experimental immunopathies, i.e., experimental allergic encephalitis and adjuvant arthritis, and the formation of humoral (IgE-like) antibody. (Martel, R.R., et al., Can. J. Physio. Pharmacol., 55: 48-51, 1977) It has also been reported recently that rapamycin inhibits murine T cell activation, apparently through a different mechanism from both FK506 and cyclosporin. Thus, both FK506 and cyclosporin were found to act at an early stage of the immune response by blocking the formation of IL-2. Rapamycin, on the other hand, did not block the formation of IL-2 but acted at a later stage of the immune response by inhibiting the response of T cells to growth-promoting lymphokines. (Staruch, M.J., et al., The FASEB Journal, Vol 3, No. 3, abstract #3411, 1989). In addition, it was disclosed that rapamycin blocks the immunosuppressive effect of FK506 but not that of cyclosporin A (Dumont, F.J. et al., The FASEB Journal, Vol. 3, No. 4, abstract #5256, 1989). There was no teaching or suggestion in these reports, however, that rapamycin could or should be used to effectively inhibit organ or tissue transplant rejection in mammals. Furthermore, these reports do not disclose or intimate that the toxic side-effects associated with FK506, and other immunosuppressive agents, would not likewise arise from administering rapamycin as an agent to inhibit transplant rejection in transplant operations.

It is an object of this invention to provide a medicament for increasing allograft acceptance (or inhibiting organ or tissue transplant rejection) in mammals by using an efficacious compound of low toxicity for its preparation.

It is another object of this invention to reduce the toxicity of other conventional chemotherapeutic agents for inhibiting transplant rejection by combining them with an efficacious compound of low toxicity.

These and other objects of the invention will become clearer in light of the detailed description which follows.

The present inventor has discovered that rapamycin can be used for the preparation of a medicament for inhibiting organ or tissue transplant rejection in a mammal in need thereof.

The present inventor has also discovered a pharmaceutical composition comprising (a) rapamycin in combination with (b) one or more other chemotherapeutic agents for inhibiting transplant rejection selected from the group consisting of azathioprine, corticosteroids, cyclosporin and FK-506.

The present invention provides the use of rapamycin for the preparation of a medicament for inhibiting organ or tissue transplant rejection in a mammal in need thereof.

As used herein, the terms "inhibiting organ or tissue transplant rejection" and "maintain inhibition of transplant rejection" refer to increasing organ or tissue transplant acceptance (or decreasing the likelihood of organ or tissue transplant rejection) involving allografts, i.e., transplantation of organs or tissues from donor to recipient both of whom are in the same species (intraspecific), such as Homo sapiens.

Rapamycin is an antifungal antibiotic which is extractable from a streptomycete, e.g., Streptomyces hygroscopicus. Methods for the preparation of rapamycin are disclosed in Sehgal et al., U.S. Patent Nos. 3,929,992, and 3,993,749. In addition, monoacyl and diacyl derivatives of rapamycin and methods for their preparation are disclosed by Rakhit, U.S. Patent No. 4,316,885. Furthermore, Stella et al., U.S. Patent No. 4,650,803 disclose water soluble prodrugs of rapamycin, i.e., rapamycin derivatives including the following rapamycin prodrugs: glycinate prodrugs, propionate prodrugs and the pyrrolidino butyrate prodrugs.

The present invention includes the use of natural and synthetic rapamycin, genetically engineered rapamycin and all derivatives and prodrugs of rapamycin, such as described in the aforementioned U.S. patents, U.S. Patent Nos. 3,929,992; 3,993,749; 4,316,885; and 4,650,803.

The present inventor has noted the efficacy of rapamycin in inhibiting transplant rejection, e.g., by depressing the immune system in mammals without the attendant toxic side-effects associated with other conventional immunosuppressive agents, e.g., azathioprine, corticosteroids and cyclosporin. Among such toxic side-effects are nephrotoxicity, severe leukopenia, thrombocytopenia, Cushing's Syndrome and diabetes.

It has been discovered that rapamycin reduces or inhibits allograft rejection in mammals, i.e., organ or tissue transplantation from donor to recipient of the same species. Among such transplanted organs or tissues and given illustratively, are heart, liver, kidney, spleen, lung, small bowel, pancreas, skin, and bone marrow, or a combination of any of the foregoing.

As used herein, the term "transplant rejection inhibiting amount" refers to the amount of rapamycin (or of rapamycin in combination with one or more other chemotherapeutic agents for inhibiting transplant rejection) which may be administered so as to inhibit transplant rejection in a mammal and to maintain transplant rejection inhibition, without causing severe toxic side-effects, e.g., nephrotoxicity, renal failure, etc. Those skilled in the art will appreciate that the dosage or amount of a transplant rejection inhibiting compound which is administered to a subject about to undergo or having undergone an organ or tissue transplant, will vary according to a number of factors, including individual characteristics, such as weight, age, and other factors, such as the type of organ or tissue transplanted or about to be transplanted.

In one aspect of this invention, the medicament for inhibiting organ or tissue transplant rejection is formulated for administration of rapamycin to a mammal in an amount of comprises from 0.5 to 50 mg/kg/day, preferably from 1 to 5 mg/kg/day. Further studies indicate that an effective therapeutic dose of rapamycin for inhibition of rejection comprises 0.01 to 10 mg/kg/day, and preferably 0.025 to 5 mg/kg/day. Such doses may be given intermittently, for example, every other day or every third day. When administered in combination with one or more other chemotherapeutic agents for inhibiting rejection in organ or tissue transplant , the effective therapeutic dose of rapamycin may be even less than indicated above. In another aspect, the inhibiting transplant rejection amount of rapamycin is administered for a period of time comprising from about 1 to about 180 days, or longer, as necessary. Those skilled in the art will recognize that compounds, drugs, agents, and the like, for inhibiting transplant rejection, may be administered to a subject mammal, e.g., a human, for an indefinite post-transplantation period, in some instances, for the lifetime of the subject, provided, of course, that the subject is tolerating the compound, drug, agent, etc., reasonably well without serious side-effects.

Rapamycin may be administered either orally or parenterally, e.g., intramuscularly, intraperitoneally, subcutaneously, or intravenously to a mammal subject. The preferred route of administration is oral.

According to this invention, rapamycin may be used for preparing in various pharmaceutical forms, including pharmaceutical forms suitable for parenteral injectable use, such as sterile aqueous solutions or dispersions and sterile powders for the preparation of sterile injectable solutions or dispersions. In addition, rapamycin may be used for preparing in tablets, caplets, capsules, and the like for convenient oral administration. Rapamycin may be used together with a pharmaceutically compatible or acceptable carrier, which includes by way of non-limiting example, oils, e.g., olive oil, alcohols, propylene glycol and polyethylene glycols,, and surfactants, such as Chemophor EL (BASF), and polysorbate 80.

Another useful feature of this invention resides in the use of rapamycin in combination with other conventional drugs, such as azathioprine (available from Burroughs Wellcome Co., Research Triangle Park, N.C., under the tradename Imuran®), corticosteroids (available from the Upjohn Company, Kalamazoo, Michigan, under the tradename Solu-Medrol®); cyclosporin (and cyclosporin A) (available from Sandoz Pharmaceuticals, East Hanover, New Jersey, under the tradename Sandimmune®), and also FK506, (available from Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan, under the tradename Fujimycin®). By combining rapamycin with such other conventional chemotherapeutic drugs or agents for inhibiting transplant rejection, the toxicity of the latter may be advantageously reduced in that lesser amounts of such toxic drug or agents are required in order to inhibit transplant rejection in a mammalian transplant subject either before or after transplantation, and also to maintain inhibition of transplant rejection.

Thus, the present invention provides the use of (a) rapamycin in combination with (b) one or more other chemotherapeutic agents for inhibiting transplant rejection for the preparation of a medicament for inhibiting transplant rejection and maintaining inhibition of transplant rejection. It should be understood that the amount of either (a) or (b) alone, might or might not be effective in inhibiting and maintaining transplant rejection. The combination of the two components (a) and (b), together, however, is effective to inhibit transplant rejection and to maintain inhibition of transplant rejection.

Therefore, as used herein, such "other" chemotherapeutic agents for inhibiting transplant rejection include, for example, azathioprine, corticosteroids, cyclosporin (and cyclosporin A) poly and monoclonal antilymphocyte antibodies (OKT3) and FK506, or a combination of any of the foregoing.

The various features of the invention described above, such as the type of organ or tissue which is transplanted; the amount effective to inhibit transplant rejection and to maintain inhibition of transplant rejection; the mode or route of administration; and the duration of treatment; apply to the use of rapamycin in combination with one or more other chemotherapeutic agents for inhibiting transplant rejection and to maintain inhibition of transplant rejection.

In addition, however, it should be understood that such other chemotherapeutic agents may be administered continuously or intermittently with rapamycin. Furthermore, the route of administration may differ from that employed for rapamycin. That is to say, such other chemotherapeutic agents may be administered parenterally while rapamycin is being administered orally to the mammalian subject.

The present invention is described below in specific working examples which are intended to illustrate the invention without limiting its scope.

EXAMPLE 1: ORGAN ALLOGRAFT STUDIES

Rats: Heterotopic heart allografts were performed from DA donor to PVG recipients. DA and PVG refer to specific rat strains. Rapamycin was administered intramuscularly in olive oil for the first 10 postoperative days except for Group 6 which only received the drug on days 3-6 postoperatively. Graft survival was assessed by daily palpation.

Large Animals: On the basis of the initial toxicity study two experiments were considered suitable to test whether rapamycin was immunosuppressive, namely, a short term dosing in dogs following renal transplantation and indefinite dosing of pigs, again following renal grafting.

Pigs: In pigs an orthotopic renal transplantation model was used and Mixed Lymphocyte Cultures (MLC) were performed to confirm histoincompatibility between donor and recipient. Untreated controls mean survival time is less than 10 days. Rapamycin was administered at a dose of 2mg/kg orally daily commencing on the first postoperative day.

Results: Allograft Studies Rat: For the rat, survival of allografts is shown in Table 1.

TABLE 1

SURVIVAL OF HETEROTOPIC CARDIAC ALLOGRAFTS IN RATS			
Group 1	No. Rats	Dose Schedule	Survival (days)
1	4	50mg/kg x 10d	75*, 88*, 100(x2)
2	4	10mg/kg x 10d	65, 77, 88, 100
3	4	2mg/kg x 10d	58, 59, 59, 66
4	4	1mg/kg x 10d	34, 49, 52, 55
5	4	0.5mg/kg x 10d	19, 20, 20, 35
6	5	10mg/kg d3-6	15, 19, 19, 19, 21
N.B. Rapamycin was administered intramuscularly in olive oil. (18mg/ml and 10mg/ml suspensions used.) Rat strains used: DA donors in PVG recipients. control rejection time (n=10) = 7.4 days.			

Explanation of Table 1: Heterotopic heart allografts in the neck of the rats were performed from DA donors to PVG recipients using the surgical techniques previously described (Heron, I., Acta. Pathol. Microbiol. Scand. 79:366, 1971). Rapamycin was dissolved in olive oil at a maximum concentration of 15 mg/ml and administered by daily intramuscular injection at dose schedules varying from 0.5 mg/kg to 50 mg/kg for ten consecutive days and in the last group at 10 mg/kg on days 3 to 6. Graft survival was assessed by daily palpation of the heart.

Rapamycin prolonged allograft survival at all doses tested. Although there was some loss of weight this was not as marked as that found when FK506 was administered to rats.

Dogs

In dogs dosing at all levels induced a vasculitis and at doses greater than 0.25 mg/kg this led to such severe manifestations that they were killed before the end of the 28 day study. At the higher doses the vasculitis affected the gastrointestinal tract, interestingly, it also caused a thrombocytopaenia. Marked depletion of cells in the lymphoid tissue, particularly B cells, occurred. In the dog, toxicity due to a vasculitis, that appears to have a particular predilection for the gastrointestinal tract, made it impossible to assess the immunosuppressive effects of the drug in this particular model. This species-specific reaction to rapamycin confirmed similar unpublished observations of the inventor and his associates.

Pigs

Survival and cause of death are shown in Table 2 with current creatinine values.

TABLE 2

SURVIVAL OF PIG ALLOGRAFTS RECEIVING RAPAMYCIN 2mg/kg/DAY ORALLY IN DAYS AND CURRENT CREATININE

	SURVIVAL	RENAL HISTOLOGY	CREATININE	OUTCOME	CAUSE OF DEATH	DAY LAST BLED
1	>51		217	ALIVE		43
2	>88		193	ALIVE		62
3	>72		283	ALIVE		64
4	4	ACUTE REJECTION	1,410	DIED	REJECTION	4
5	5	INFARCTION		DIED	INFARCTION	5
6	40	FOCAL PYELONEPHRITIS	161	DIED	INTERSTITIAL PNEUMONITIS	47
7	49	MILD ATN	235	DIED	INTERSTITIAL PNEUMONITIS	48
8	50	MILD ATN	176	DIED	INTERSTITIAL PNEUMONITIS	48
9	55	EARLY MILD REJECTION	239	DIED	INTERSTITIAL PNEUMONITIS	51
10	63	MODERATE ATN	283	DIED	INTERSTITIAL PNEUMONITIS	63

Explanation of Table 2: Orthotopic kidney transplantation with contralateral nephrectomy was performed in the pig, as previously described (Calne, R.Y. et al., Brit. J. Surg., 59: 969-977 (1972). Donor and recipient pairs were obtained from litters with different parents and incompatibility at the Major Histocompatibility Complex (MHC) was confirmed by the mixed lymphocyte reaction (Bradley, B.A., et al., Tissue Antigens, 4: 283-290, 1974). Rapamycin was administered orally at 2 mg/kg/day dissolved in olive oil at a concentration of 10 mg/ml.

In the case of pigs, one died of accelerated acute rejection and one died due to technical failure. The remaining eight animals recovered well and after an initial weight loss of approximately 10%. Subsequently, at about day 50 5 animals developed anorexia, diarrhea and became unwell to the extent that it was decided that they should be killed. Histological examination of these animals revealed that they were suffering from interstitial pneumonitis, probably due to over-immunosuppression, and this was the reason that they became unwell. Furthermore, the renal histology did not

show evidence of rejection except a mild degree in one animal who had not received the drug for 4 days. Histological examination of the colons in these animals showed mucosal and submucosal edema but no vasculitis and no ulceration. Thus this was probably secondary to the systemic effects of the pneumonitis. The remaining three animals continued to thrive, all dosing having being stopped as indicated in Table 3.

Discussion

Rapamycin was immunosuppressive and not toxic in the rat down to a dose of 0.5mg/kg although the compound was more effective at higher doses.

In pigs, the results of the toxicity study showed that the drug was tolerated at a dose of 1 mg/kg in that both animals gained weight. On histological examination colitis was seen but no vasculitis was found or suggested. Rapamycin was effective as an immunosuppressive agent but after about 50 days of continuous dosing at 2 mg/kg, 50% of the animals developed interstitial pneumonitis due to over-immunosuppression, and these animals were killed. However, none of the animals showed any evidence of ulceration in the colon or vasculitis. Therefore, in future studies monitoring of blood drug levels will be of benefit.

In conclusion, rapamycin is a very effective immunosuppressive agent which can be employed to inhibit allograft transplantation rejection in mammalian subjects.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Use of rapamycin for the preparation of a medicament for inhibiting organ or tissue transplant rejection in a mammal in need thereof.

2. Use of rapamycin according to claim 1, wherein the medicament further serves to maintain said inhibition of organ or tissue transplant rejection.

3. Use of rapamycin according to claim 1 or 2, wherein the medicament further contains an amount of one or more other chemotherapeutic agents for inhibiting organ or tissue transplant rejection in a mammal in need thereof.

4. Use of rapamycin according to claim 3, wherein said chemotherapeutic agent is selected from the group consisting of azathioprine, corticosteroids, cyclosporin, FK506, OKT3 and combinations of any of the foregoing.

5. Use of rapamycin according to any one of claims 1 to 4, wherein said medicament is formulated for administration of rapamycin to said mammal in an amount of from 0.5 to 50 mg/kg/day.

6. Use of rapamycin according to claim 5, wherein said medicament is formulated for administration of rapamycin to said mammal in an amount of from 1 to 5 mg/kg/day.

7. Use of rapamycin according to any one of claims 1 to 4, wherein said medicament is formulated for administration of rapamycin to said mammal in an amount of from 0.01 to 10 mg/kg/day.

8. Use of rapamycin according to claim 7, wherein said amount is from 0.025 to 5 mg/kg/day.

9. The use of rapamycin according to any one of claims 1 to 8, wherein said medicament is formulated for administration of rapamycin in an oral dosage form.

10. The use of rapamycin according to any one of claims 1 to 9, wherein said medicament is formulated for administration of rapamycin in a parenteral dosage form.

11. A pharmaceutical composition for use as a medicament comprising a combination of (a) rapamycin and (b) one or more chemotherapeutic agents selected from the group consisting of azathioprine, corticosteroids, cyclosporin and FK-506.

Claims for the following Contracting State : ES

1. A method of preparing a pharmaceutical composition for use as a medicament comprising combining (a) rapamycin and (b) one or more chemotherapeutic agents selected from the group consisting of azathioprine, corticosteroids, cyclosporin and FK-506.

2. Use of rapamycin for the preparation of a medicament for inhibiting organ or tissue transplant rejection in a mammal in need thereof.

3. Use of rapamycin according to claim 2, wherein the medicament further serves to maintain said inhibition of organ or tissue transplant rejection.

4. Use of rapamycin according to claim 2 or 3, wherein the medicament further contains an amount of one or more other chemotherapeutic agents for inhibiting organ or tissue transplant rejection in a mammal in need thereof.

5. Use of rapamycin according to claim 4, wherein said chemotherapeutic agent is selected from the group consisting of azathioprine, corticosteroids, cyclosporin, FK506, OKT3 and combinations or any of the foregoing.

6. Use of rapamycin according to any one of claims 2 to 5, wherein said medicament is formulated for administration of rapamycin to said mammal in an amount of from 0.5 to 50 mg/kg/day.

7. Use of rapamycin according to claim 6, wherein said medicament is formulated for administration of rapamycin to said mammal in an amount of from 1 to 5 mg/kg/day.

8. Use of rapamycin according to any one of claims 2 to 5, wherein said medicament is formulated for administration of rapamycin to said mammal in an amount of from 0.01 to 10 mg/kg/day.

9. Use of rapamycin according to claim 8, wherein said amount is from 0.025 to 5 mg/kg/day.

10. The use of rapamycin according to any one of claims 2 to 9, wherein said medicament is formulated for administration of rapamycin in an oral dosage form.

11. The use of rapamycin according to any one of claims 2 to 10, wherein said medicament is formulated for administration of rapamycin in a parenteral dosage form.

Claims for the following Contracting State : GR

1. Use of rapamycin for the preparation of a medicament for inhibiting organ or tissue transplant rejection in a mammal in need thereof.

2. Use of rapamycin according to claim 1, wherein the medicament further serves to maintain said inhibition of organ or tissue transplant rejection.

3. Use of rapamycin according to claim 1 or 2, wherein the medicament further contains an amount of one or more other chemotherapeutic agents for inhibiting organ or tissue transplant rejection in a mammal in need thereof.

4. Use of rapamycin according to claim 3, wherein said chemotherapeutic agent is selected from the group consisting of azathioprine, corticosteroids, cyclosporin, FK506, OKT3 and combinations or any of the foregoing.

5. Use of rapamycin according to any one of claims 1 to 4, wherein said medicament is formulated for administration of rapamycin to said mammal in an amount of from 0.5 to 50 mg/kg/day.

6. Use of rapamycin according to claim 5, wherein said medicament is formulated for administration of rapamycin to said mammal in an amount of from 1 to 5 mg/kg/day.

7. Use of rapamycin according to any one of claims 1 to 4, wherein said medicament is formulated for administration of rapamycin to said mammal in an amount of from 0.01 to 10 mg/kg/day.

8. Use of rapamycin according to claim 7, wherein said amount is from 0.025 to 5 mg/kg/day.

9. The use of rapamycin according to any one of claims 1 to 8, wherein said medicament is formulated for administration of rapamycin in an oral dosage form.

10. The use of rapamycin according to any one of claims 1 to 9, wherein said medicament is formulated for administration of rapamycin in a parenteral dosage form.

11. A method of preparing a pharmaceutical composition for use as a medicament comprising combining (a) rapamycin and (b) one or more chemotherapeutic agents selected from the group consisting of azathioprine, corticosteroids, cyclosporin and FK-506.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Verwendung von Rapamycin für die Herstellung eines Medikamentes zum Inhibieren einer Organ- oder Gewebetransplantatabstoßung in einem Säugetier, das dessen bedarf.

2. Verwendung von Rapamycin nach Anspruch 1, wobei das Medikament weiter dazu dient, die Inhibition der Organ- oder Gewebetransplantatabstoßung aufrecht zu erhalten.

3. Verwendung von Rapamycin nach Anspruch 1 oder 2, wobei das Medikament weiter eine Menge von einem oder mehreren chemotherapeutischen Agenzien zum Inhibieren der Organ- oder Gewebetransplantatabstoßung in einem Säugetier, das dessen bedarf, enthält.

4. Verwendung von Rapamycin nach Anspruch 3, wobei das chemotherapeutische Agenz aus der Gruppe ausgewählt ist, die aus Azathioprin, Corticosteroiden, Cyclosporin, FK506, OKT3 und Kombinationen der zuvor genannten besteht.

5. Verwendung von Rapamycin nach einem der Ansprüche 1 bis 4, wobei das Medikament für die Verabreichung von Rapamycin an das Säugetier in einer Menge von 0,5 bis 50 mg/kg/Tag formuliert ist.

6. Verwendung von Rapamycin nach Anspruch 5, wobei das Medikament für die Verabreichung von Rapamycin an das Säugetier in einer Menge von 1 bis 5 mg/kg/Tag formuliert ist.

7. Verwendung von Rapamycin nach einem der Ansprüche 1 bis 4, wobei das Medikament für die Verabreichung von Rapamycin an das Säugetier in einer Menge von zwischen 0,01 bis 10 mg/kg/Tag formuliert ist.

8. Verwendung von Rapamycin nach Anspruch 7, wobei die Menge von 0,025 bis 5 mg/kg/Tag beträgt.

9. Verwendung von Rapamycin nach einem der Ansprüche 1 bis 8, wobei das Medikament für die Verabreichung von Rapamycin in einer oralen Dosierungsform formuliert ist.

10. Verwendung von Rapamycin nach einem der Ansprüche 1 bis 9, wobei das Medikament für die Verabreichung von Rapamycin in einer parenteralen Dosierungsform formuliert ist.

11. Pharmazeutische Zusammensetzung zur Verwendung als Medikament, umfassend eine Kombination von (a) Rapamycin und (b) einem oder mehreren chemotherapeutischen Agenzien, die aus der aus Azathioprin, Corticosteroiden, Cyclosporin und FK506 bestehenden Gruppe ausgewählt sind.

Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zum Herstellen einer pharmazeutischen Zusammensetzung zur Verwendung als ein Medikament, umfassend das Vereinen von (a) Rapamycin und (b) einem oder mehreren chemotherapeutischen Agenzien, die aus der aus Azathioprin, Corticosteroiden, Cyclosporin und FK506 bestehenden Gruppe ausgewählt sind.

2. Verwendung von Rapamycin für die Herstellung eines Medikamentes zum Inhibieren der Organ- oder Gewebetransplantatabstoßung in einem Säugetier, das dessen bedarf.

3. Verwendung von Rapamycin nach Anspruch 2, wobei das Medikament weiter dazu dient, die Inhibition der Organ- oder Gewebetransplantatabstoßung aufrecht zu erhalten.

4. Verwendung von Rapamycin nach Anspruch 2 oder 3, wobei das Medikament weiter eine Menge von einem oder mehreren anderen chemotherapeutischen Agenzien zum Inhibieren der Organ- oder Gewebetransplantatabstoßung in einem Säugetier, das dessen bedarf, enthält.

5. Verwendung von Rapamycin nach Anspruch 4, wobei das chemotherapeutische Mittel aus der Gruppe ausgewählt ist, die aus Azathioprin, Corticosteroiden, Cyclosporin, FK506 oder OKT3 und Kombinationen der zuvor genannten besteht.

6. Verwendung von Rapamycin nach einem der Ansprüche 2 bis 5, wobei das Medikament für die Verabreichung von Rapamycin an das Säugetier in einer Menge von 0,5 bis 50 mg/kg/Tag formuliert ist.

7. Verwendung von Rapamycin nach Anspruch 6, wobei das Medikament für die Verabreichung von Rapamycin an das Säugetier in einer Menge von 1 bis 5 mg/kg/Tag formuliert ist.

8. Verwendung von Rapamycin nach einem der Ansprüche 2 bis 5, wobei das Medikamt für die Verabreichung von Rapamycin an das Säugetier in einer Menge von 0,01 bis 10 mg/kg/Tag formuliert ist.

9. Verwendung von Rapamycin nach Anspruch 8, wobei die Menge von 0,025 bis 5 mg/kg/Tag beträgt.

10. Verwendung von Rapamycin nach einem der Ansprüche 2 bis 9, wobei das Medikament für die Verabreichung von Rapamycin in einer oralen Dosierungsform formuliert ist.

11. Verwendung von Rapamycin nach einem der Ansprüche 2 bis 10, wobei das Medikament für die Verabreichung von Rapamycin in einer parenteralen Dosierungsform formuliert ist.

Patentansprüche für folgenden Vertragsstaat : GR

1. Verwendung von Rapamycin für die Herstellung eines Medikamentes zum Inhibieren einer Organ- oder Gewebetransplantatabstoßung in einem Säugetier, das dessen bedarf.

2. Verwendung von Rapamycin nach Anspruch 1, wobei das Medikament weiter dazu dient, die Inhibition der Organ- oder Gewebetransplantatabstoßung aufrecht zu erhalten.

3. Verwendung von Rapamycin nach Anspruch 1 oder 2, wobei das Medikament weiter eine Menge von einem oder mehreren anderen chemotherapeutischen Agenzien zum Inhibieren der Organ- oder Gewebetransplantatabstoßung in einem Säugetier, das dessen bedarf, enthält.

4. Verwendung von Rapamycin nach Anspruch 3, wobei das chemotherapeutische Agenz aus der Gruppe ausgewählt ist, die aus Azathioprin, Corticosteroiden, Cyclosporin, FK506, OKT3 und Kombinationen der zuvor genannten besteht.

5. Verwendung von Rapamycin nach einem der Ansprüche 1 bis 4, wobei das Medikament für die Verabreichung von Rapamycin an das Säugetier in einer Menge von 0,5 und 50 mg/kg/Tag formuliert ist.

6. Verwendung von Rapamycin nach Anspruch 5, wobei das Medikament für die Verabreichung von Rapamycin an das Säugetier in einer Menge von 1 bis 5 mg/kg/Tag formuliert ist.

7. Verwendung von Rapamycin nach einem der Ansprüche 1 bis 4, wobei das Medikament für die Verabreichung von Rapamycin an das Säugetier in einer Menge von 0,01 bis 10 mg/kg/Tag formuliert ist.

8. Verwendung von Rapamycin nach Anspruch 7, wobei die Menge von 0,025 bis 5 mg/kg/Tag beträgt.

9. Verwendung von Rapamycin nach einem der Ansprüche 1 bis 8, wobei das Medikament für die Verabreichung von Rapamycin in einer oralen Dosierungsform formuliert ist.

10. Verwendung von Rapamycin nach einem der Ansprüche 1 bis 9, wobei das Medikament für die Verabreichung von Rapamycin in einer parenteralen Dosierungsform formuliert ist.

11. Verfahren zum Herstellen einer pharmazeutischen Zusammensetzung zur Verwendung als ein Medikament, umfassend das Vereinen von (a) Rapamycin und (b) einem oder mehreren chemotherapeutischen Agenzien, die aus der aus Azathioprin, Corticosteroiden, Cyclosporin und FK506 bestehenden Gruppe ausgewählt sind.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Utilisation de rapamycine pour la préparation d'un médicament destiné à inhiber le rejet d'une greffe d'organe ou de tissu chez un mammifère en ayant besoin.

2. Utilisation de rapamycine selon la revendication 1, dans laquelle le médicament sert en outre à prolonger ladite inhibition du rejet d'une greffe d'organe ou de tissu.

3. Utilisation de rapamycine selon la revendication 1 ou 2, dans laquelle le médicament contient en outre une quantité d'un ou de plusieurs agents chimiothérapeutiques destinés à inhiber le rejet d'une greffe d'organe ou de tissu chez un mammifère en ayant besoin.

4. Utilisation de rapamycine selon la revendication 3, dans laquelle ledit agent chimiothérapeutique est choisi dans le groupe consistant en azathioprine, corticostéroïdes, cyclosporine, FK506, OKT3 et les combinaisons de ceux-ci.

5. Utilisation de rapamycine selon l'une des revendications 1 à 4, dans laquelle ledit médicament est formulé pour l'administration de rapamycine audit mammifère dans une quantité de 0,5 à 50 mg/kg/jour.

6. Utilisation de rapamycine selon la revendication 5, dans laquelle ledit médicament est formulé pour l'administration de rapamycine audit mammifère dans une quantité de 1 à 5 mg/kg/jour.

7. Utilisation de rapamycine selon l'une des revendications 1 à 4, dans laquelle ledit médicament est formulé pour l'administration de rapamycine audit mammifère dans une quantité de 0,01 à 10 mg/kg/jour.

8. Utilisation de rapamycine selon la revendication 7, dans laquelle ladite quantité est de 0,025 à 5 mg/kg/jour.

9. Utilisation de rapamycine selon l'une des revendications 1 à 8, dans laquelle ledit médicament est formulé pour l'administration de rapamycine sous une forme pharmaceutique orale.

10. Utilisation de rapamycine selon l'une des revendications 1 à 9, dans laquelle ledit médicament est formulé pour l'administration de rapamycine sous une forme pharmaceutique parentérale.

11. Composition pharmaceutique destinée à être utilisée en tant que médicament comprenant une combinaison de (a) rapamycine et (b) d'un ou de plusieurs agents chimiothérapeutiques choisis dans le groupe consistant en azathioprine, corticostéroïdes, cyclosporine et FK506.

Revendications pour l'Etat contractant suivant : ES

1. Procédé de préparation d'une composition pharmaceutique destinée à être utilisée en tant que médicament comprenant une combinaison de (a) rapamycine et (b) d'un ou de plusieurs agents chimiothérapeutiques choisis dans le groupe consistant en azathioprine, corticostéroïdes, cyclosporine et FK506.

2. Utilisation de rapamycine pour la préparation d'un médicament destiné à inhiber le rejet d'une greffe d'organe ou de tissu chez un mammifère en ayant besoin.

3. Utilisation de rapamycine selon la revendication 2, dans laquelle le médicament sert en outre à prolonger ladite inhibition du rejet d'une greffe d'organe ou de tissu.

4. Utilisation de rapamycine selon la revendication 2 ou 3, dans laquelle le médicament contient en outre une quantité d'un ou de plusieurs agents chimiothérapeutique destinés à inhiber le rejet d'une greffe d'organe ou de tissu chez un mammifère en ayant besoin.

5. Utilisation de rapamycine selon la revendication 4, dans laquelle ledit agent chimiothérapeutique est choisi dans le groupe consistant en azathioprine, corticostéroïdes, cyclosporine, FK506, OKT3 et les combinaisons de ceux-ci.

6. Utilisation de rapamycine selon l'une des revendications 2 à 5, dans laquelle ledit médicament est formulé pour l'administration de rapamycine audit mammifère dans une quantité de 0,5 à 50 mg/kg/jour.

7. Utilisation de rapamycine selon la revendication 6, dans laquelle ledit médicament est formulé pour l'administration de rapamycine audit mammifère dans une quantité de 1 à 5 mg/kg/jour.

8. Utilisation de rapamycine selon l'une des revendications 2 à 5, dans laquelle ledit médicament est formulé pour l'administration de rapamycine audit mammifère dans une quantité de 0,01 à 10 mg/kg/jour.

9. Utilisation de rapamycine selon la revendication 8, dans laquelle ladite quantité est de 0,025 à 5 mg/kg/jour.

10. Utilisation de rapamycine selon l'une des revendications 2 à 9, dans laquelle ledit médicament est formulé pour l'administration de rapamycine sous une forme pharmaceutique orale.

11. Utilisation de rapamycine selon l'une des revendications 2 à 10, dans laquelle ledit médicament est formulé pour l'administration de rapamycine sous une forme pharmaceutique parentérale.

Revendications pour l'Etat contractant suivant : GR

1. Utilisation de rapamycine pour la préparation d'un médicament destiné à inhiber le rejet d'une greffe d'organe ou de tissu chez un mammifère en ayant besoin.

2. Utilisation de rapamycine selon la revendication 1, dans laquelle le médicament sert en outre à prolonger ladite inhibition du rejet d'une greffe d'organe ou de tissu.

3. Utilisation de rapamycine selon la revendication 1 ou 2, dans laquelle le médicament contient en outre une quantité d'un ou de plusieurs agents chimiothérapeutiques destinés à inhiber le rejet d'une greffe d'organe ou de tissu chez un mammifère en ayant besoin.

4. Utilisation de rapamycine selon la revendication 3, dans laquelle ledit agent chimiothérapeutique est choisi dans le groupe consistant en azathioprine, corticostéroïdes, cyclosporine, FK506, OKT3 et les combinaisons de ceux-ci.

5. Utilisation de rapamycine selon l'une des revendications 1 à 4, dans laquelle ledit médicament est formulé pour l'administration de rapamycine audit mammifère dans une quantité de 0,5 à 50 mg/kg/jour.

6. Utilisation de rapamycine selon la revendication 5, dans laquelle ledit médicament est formulé pour l'administration de rapamycine audit mammifère dans une quantité de 1 à 5 mg/kg/jour.

7. Utilisation de rapamycine selon l'une des revendications 1 à 4, dans laquelle ledit médicament est formulé pour l'administration de rapamycine audit mammifère dans une quantité de 0,01 à 10 mg/kg/jour.

8. Utilisation de rapamycine selon la revendication 7, dans laquelle ladite quantité est de 0,025 à 5 mg/kg/jour.

9. Utilisation de rapamycine selon l'une des revendications 1 à 8, dans laquelle ledit médicament est formulé pour l'administration de rapamycine sous une forme pharmaceutique orale.

10. Utilisation de rapamycine selon l'une des revendications 1 à 9, dans laquelle ledit médicament est formulé pour l'administration de rapamycine sous une forme pharmaceutique parentérale.

11. Procédé de préparation d'une composition pharmaceutique destinée à être utilisée en tant que médicament comprenant une combinaison de (a) rapamycine et (b) d'un ou de plusieurs agents chimiothérapeutiques choisis dans le groupe consistant en azathioprine, corticostéroïdes, cyclosporine et FK506.